

of them. We will do well to scrutinize each detail of early infant care to determine if it fulfills a physiological optimum or constitutes simply a compromise of the normal with hospital, obstetric, and pediatric convenience. Such errors as may have crept into the management of this period are certainly not chargeable directly to the obstetrician, for the time which has wrought these changes has been one in which the pediatrician has assumed constantly increasing responsibility in the nursery.

From the standpoint of the pediatrician, at least of this pediatrician, it seems desirable that attempts be made to modify the care of the newborn infant in the following direction:

1. Mothers should receive a minimum of medication as a preliminary to delivery compatible with relative freedom from severe pain.

2. Chemotherapeutic and anti-biotic substitutes for Cr  d   prophylaxis should promptly be explored and introduced.

3. Maternal nursing should be re-accepted as the normal method of feeding and honest efforts made to encourage it, not to defeat it.

4. Added opportunity should be provided for mother and infant to effect an acquaintance and adaptation during the lying-in period.

5. Circumcision should not be proposed as a medical necessity unless better justification for it can be advanced.

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Typhus Fever in the Second World War*

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IN most of the previous conflicts on the European continent, typhus fever caused enormous suffering and loss of life among soldiers and civilians. Because it had played a decisive role in many military campaigns of the past, typhus was regarded at the outbreak of the second World War as one of the most dangerous of the potential epidemic diseases which were expected to occur during or after the war. Although its toll among civilians in certain regions has indeed been considerable in the years 1939 to 1946, the recent developments in our knowledge of its prevention and control have achieved such remarkable results that the discussion of these developments at some length now seems pertinent. In order to provide a background for an appreciation of the new methods of combating typhus, I shall review the history of typhus and then describe the events in the second World War as they bear on our subject.

Hirsch, in his account of historical pathology says:

"The history of typhus is written in those dark pages of the world's story which tell of the grievous visitations of mankind by war, famine, and misery of every kind. In every age, as far back as the historical inquirer can follow the disease at all, typhus is met with in association with the saddest misfortunes of the populace; and it is, therefore, a well-grounded surmise that the numerous pestilences of war and famine in ancient times and in the Middle Ages, which are known to us, not from medical sources but merely from the chronicles, had included typhus fever as a prominent figure among them."¹

The earliest scientific discussion of typhus probably is

that of Fracastorius in his famous "De Contagione et Contagiosis Morbis" published in 1546.² The existence of other epidemic diseases, such as plague, relapsing fever, smallpox, and typhoid, at one and the same time with typhus had made difficult its recognition as a separate entity. Even the description of Fracastorius is confusing in certain respects, and not until 1837, almost 300 years later, were typhus and typhoid clearly differentiated for the medical profession by an American physician, W. W. Gerhard.³

In the history of Europe after the fifteenth century, there is no difficulty in finding reports of many outbreaks which most certainly were typhus fever. As early as 1489 the Spanish soldiers who had fought against the Turks in Cyprus brought typhus to Spain. At the siege of Granada 17,000 men in Ferdinand and Isabella's army died of typhus, almost six times the number killed in combat with the Moors.⁴ Soon thereafter typhus appeared in Italy, where Fracastorius had occasion to study its characteristics. In 1528 the French army besieging Naples was at the point of decisive victory over the forces of Charles V, a victory which would have had enormous effects on the subsequent developments in Europe. But then, as Zinsser put it, "typhus made its political debut . . . by one of the most far-reaching and profoundly effective strokes of its entire career . . ."⁵ With great rapidity it struck down 30,000 soldiers in the camps of the French, and the remnants of the army were forced to withdraw.

During this period the battles in the Balkans contributed greatly to the spread of typhus across the continent of Europe. Large forces were assembled from various parts of Germany, Italy, and France and were sent against the Turks, but many of the men fell victims to typhus before they reached the battlefields. The disease became known as the "Morbis Hungaricus" as it was disseminated throughout Europe by the soldiers returning from Hungary.⁶

During the seventeenth century typhus continued its exploits in the almost incessant military struggles of that era, affecting civilians and soldiers alike. During the Thirty Years' War, when the Swedish army under Gustavus Adol-

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phus was about to launch a campaign against Wallenstein at Nuremberg in 1632, typhus, aided by scurvy, killed 18,000 soldiers and forced both armies to withdraw.⁵

In the century and a half between the Thirty Years' War and the Napoleonic campaigns, typhus contributed almost continuously to the chronicles of epidemic disease. In the invasion of Russia in 1812, typhus was one of the major factors in the disaster which befell Napoleon's army of half a million men. Prinzing gives this account of the campaign: "... When Napoleon's army withdrew from Moscow it left behind several thousand typhus fever patients, almost all of whom died—only the stronger patients were taken along on wagons . . . In Vilna, which was greatly overcrowded, typhus fever raged furiously. The large number of sick and exhausted soldiers that were left behind, owing to the extreme cold . . . sought shelter, partly in private homes, and partly in hospitals. The latter were in a terrific condition; sick men and dead men were packed together in the cold unheated rooms, the former lying on rotten straw, completely deserted, and without care or nourishment. The few unfortunate soldiers who had survived the awful misery of the march, hungry, clothed in rags, with torn shoes, alive with vermin, with frozen and gangrenous limbs, scattered in all directions, some going home, and others to strongholds that were in the hands of the French."⁷

From 1812 we pass over another hundred years to the first World War and find typhus again striking frightfully in Serbia^{8,9} and later in Russia.¹⁰ Estimates place the number of cases of typhus fever in Russia as high as thirty million in the years 1918-22 and deaths as many as three million. Typhus probably has taken as many lives in the past 400 years as have all the weapons of war in the battles of these blood-drenched centuries.

After surveying this impressive record, it will be of interest to inquire more closely into the characteristics of typhus fever. What was known of its etiology, transmission, prevention, control, and treatment at the outbreak of the second World War?

STATUS OF KNOWLEDGE OF TYPHUS IN 1939

Etiology. The micro-organism which causes classical epidemic typhus fever was described in 1916 and was given the name of *Rickettsia prowazeki*, which honors two of the early investigators who contracted typhus and died. Dr. H. T. Ricketts, an American, and Dr. S. von Prowazek, an Austrian.¹¹ The term "rickettsial disease" is now applied not only to typhus fever, but also to several other human diseases which are similar clinically to typhus and which are caused by other rickettsiae. *Rickettsiae prowazeki* are pleomorphic cocco-bacillary forms which multiply inside certain cells of susceptible hosts. In the classification of micro-organisms, rickettsiae occupy a position between bacteria and viruses.

In addition to classical epidemic typhus fever, another form is now recognized—murine typhus fever. The etiologic agent has been named *Rickettsia mooseri*¹² in honor of the Swiss physician who observed the micro-organisms in the cells of infected guinea pigs. Murine typhus is world wide in distribution, occurring sporadically as a relatively mild disease with a low mortality. The relationship of murine to classical epidemic typhus is most interesting but our attention in this discussion

will be restricted entirely to a consideration of classical typhus fever.

Transmission. In 1909, Nicolle, Comte, and Conseil discovered that typhus is transmitted by the body louse, *Pediculus humanus corporis*.¹³ *Rickettsiae prowazeki* are present in the blood of patients suffering from typhus during the febrile period of the disease. The body louse sucks blood, and the rickettsiae enter the cells lining the intestinal tract of the louse. In a few days the rickettsiae have multiplied so profusely that the cells containing them are swollen and may burst, liberating the organisms, which may then be passed in the feces of the louse or may enter still other cells. Eventually, the typhus-infected lice die of intestinal obstruction caused by the enormous swelling of the lining cells. Lice tend to leave febrile patients in favor of persons with normal temperatures, and likewise they quickly abandon a corpse and seek a new host. Each time a louse bites, it makes a small puncture in the skin, and it also defecates as it sucks blood. The site of the louse bite is somewhat irritating, and the person tends to scratch, thus rubbing the feces of the louse into the skin, probably over the puncture. This is the usual way in which the infection is passed from man to man. It is also possible to become infected by crushing an infected louse on the skin, by rubbing the infected feces into the eyes, or by having dried feces of the infected louse gain access to the conjunctivae or the mucous membranes of the respiratory tract, as an airborne infection. It is important to recall that the typhus infection in lice establishes itself after an incubation period, just as it does in man. The period of maximum danger of spread of typhus from a louse-infested patient to other persons extends into the first two weeks of convalescence when the victim becomes ambulatory. The hazard in handling corpses within a few hours after death is obvious. Once deloused and bathed, however, typhus patients are not capable of transmitting the infection to other persons by contact; *Rickettsia prowazeki* does not occur in human saliva, sputum, urine, or feces, unless blood is also present (literature reviewed in^{14,15}).

Louse control. Shortly after the role of the louse in typhus transmission was discovered, demonstrations of the efficacy of delousing in controlling epidemics of this disease were made in North Africa in 1912¹⁴ and in Serbia in 1915.⁸ It was established that effective delousing of a community stopped typhus. At that time and until very recently, the procedure for delousing required the infested persons to remove all of their clothes, which were then subjected to heat while the persons bathed. When large numbers of persons were involved, this process was very cumbersome, expensive, and time consuming. People objected to the damage done to their only garments by the heating process, particularly if moist heat was employed. Furthermore, shortages of fuel and apparatus for heating the clothing were the rule under those circumstances which fostered the outbreaks of typhus.

In addition, reinfestation of persons deloused by this method could, and usually did, occur immediately, unless very careful segregation was achieved. The conditions which predispose to louse infestation, and consequently to epidemic typhus, are shifting of populations, inadequate and temporary housing, crowding of people together, lack of facilities for bathing, and weather so cold that people tend to leave their garments on continuously day and night, for weeks or months at a time. It is obvious that under such conditions, a very efficient organization and an abundance of fuel are essential for satisfactory delousing. That this combination has been extremely difficult to obtain is grimly shown by the numerous severe epidemics of typhus which have occurred in various countries despite full appreciation of the fact that effective delousing would stop the outbreaks. More practical and rapid methods of delousing were urgently needed.

Vaccination. Following the discovery of the etiologic agent of typhus fever, many efforts were made to develop a satisfactory vaccine against the disease. These attempts were made in the face of several obstacles. First, *Rickettsia prowazeki* does not grow in the absence of living cells; cultivation of the organism was possible only in lice, or various animal tissues. Second, vaccination with living rickettsiae of murine typhus, which appeared to be a safe procedure when applied to natives in North Africa, proved to be dangerous for Europeans.¹⁶ Third, there was a real hazard in working with typhus in the laboratory. Several of the early investigators contracted typhus and died.

Contributions toward the solution of the problem of obtaining large quantities of rickettsiae had been made prior to 1939. Zinser and Castaneda¹⁷ found that x-rayed rats could be used to produce murine rickettsiae in abundance. Castaneda¹⁸ introduced the method for the preparation of murine vaccine from the lungs of rodents. Durand and Giroud¹⁹

made epidemic louse-borne rickettsial vaccine from mouse lungs. Cox^{20, 21} devised a method even more practical and satisfactory by utilizing the yolk sac membrane of developing chick embryos as a growth medium for rickettsiae of various types. But, in 1939, there was no evidence bearing on the efficacy of any of the newly developed vaccines under epidemic conditions, and it was obvious that Weigl's vaccine, made from the intestines of lice,²² was not suitable for mass production. Thus, a great deal of information was needed in regard to the recent vaccines.

Treatment. In 1939 no chemotherapeutic agents had been found for typhus. Immune serum from humans and animals had not had an impressive effect on the course of the illness. Typhus, being a disease closely associated with human misery, nearly always occurred under precisely those conditions in which the hospital facilities and medical staffs were either sorely taxed or virtually nonexistent. For this reason, relatively few studies had been made of the pathologic physiology of typhus. Indeed, the information in the classic monograph of Wolbach, Todd, and Palfrey,²³ published in 1922, had not been advanced appreciably in regard to the clinical and pathological findings in typhus.

EXTENT OF TYPHUS FEVER OUTBREAKS IN CIVILIAN POPULATIONS BETWEEN 1939 AND 1945

Having reviewed the record of typhus in order to call to mind its potentialities as a scourge, and having mentioned the principal gaps in our knowledge of certain aspects of the disease, we must agree with those who, in 1939, feared that the second World War would provide on an unprecedented scale the mass misery and famine in which typhus has always exacted its heavy toll. The figures which are available for the reported cases of typhus in certain of the countries in the war area are presented in Table 1. It may safely be assumed that these figures contain numerous inaccuracies.

TABLE 1.—Reported Cases of Typhus Fever For 1940 to 1945 Inclusive For Certain of the Countries in the War Areas.

	1940	1941	1942	1943	1944	1945
England	1	26
France	2	230	?	11?	303
Spain	14	9,560	4,144	640	498	27
Italy	699†	1,215†	198
Germany	230	2,158	2,043	5,058	2,467	18,000†
Poland	12,000*	?	?	?	?	14,000
Bulgaria	155	281	709	1,843	702	979
Rumania	1,403	1,827	3,992	8,441	6,000‡	8,244
Hungary	93	652	827	1,012	3,336	?
Greece	43	7	?	99	388	697
Yugoslavia	282	86?	?	?	8,243	2,285
Turkey	716	704	427	4,234	3,121	2,700
Iran	256	115	907	12,885	6,436	826
Egypt	3,636	9,324	32,288	40,084	18,533	15,746
Tunisia	651	7,078	16,295	356?	1,007	403
Algeria	2,146	12,827	35,205	8,321	1,770	1,024
Morocco	355	1,471	25,846	16,191	2,928	8,243
China	2,191	245	369	12?	141	1,874
Japan	2	864	?	?	?	?

The figures are compiled from the United States Public Health Reports, vols. 56-61, except as noted: * League of Nations Bulletin, vol. 10, 1942-43. † U.S.A. Typhus Commission files. ‡ Reports for year incomplete.

Observers who were present during some of the outbreaks are well aware of the inadequacy of the case reporting facilities and of the unwillingness of officials in some places to admit the extent of the typhus problem in their areas. Despite inaccuracies, however, the table provides us with much information.

Several points should be emphasized. Some of the countries in which typhus had appeared each winter in outbreaks of small size before 1939 experienced large increases in the war years, for example, Morocco, Algeria, Tunisia, Egypt, Iran, Turkey, Yugoslavia, and probably Poland, although information from the areas occupied by the Germans and the Russians is incomplete.

Typhus appeared in epidemic form in a few countries usually free of the disease, notably Spain, Italy, and Germany. The cases reported for England and France occurred largely in repatriated persons who traveled to those countries during the incubation period of the disease.

A glance at the figures for the years 1940 and 1941 shows that the areas in which Allied operations occurred in late 1942 were suffering from severe outbreaks. Our troops were exposed to the risk of infection by contact with native populations. Furthermore, our forces entered Naples in October, 1943, just as that badly overcrowded and heavily bombed city was being thoroughly seeded with epidemic typhus. In the same year our troops stationed in Iran and in Egypt were exposed to the infection that was at its height in those countries.

In 1944 the operations of the Yugoslav forces which were effectively pinning down several divisions of the German army were severely handicapped by the spread of typhus not only among the civilian populations but also in the Yugoslav army itself.

In 1945 as the Allied armies reached and passed the Siegfried Line, typhus was encountered among the "slave laborers" and among the residents of the city of Cologne. Many of the German camps containing prisoners of war were found to have active typhus cases at the time the inmates were liberated. But by far the most serious situations were found in the notorious concentration camps where the Germans had assembled political prisoners as well as ordinary criminals from all parts of the continent. The incredibly horrible conditions existing in Buchenwald, Belsen, Dachau, Mauthausen, Flossenbürg, and Vaihingen, to mention a few, have been described in the press and discussed in some of the war crime trials. Typhus contributed to the horrors of these camps. It is probable that more than 90 per cent of all the typhus cases in Germany and Austria in 1945 occurred among the inmates of the concentration camps. As the German armies retreated, they tried at first to take all their prisoners to rear areas, and they succeeded in transferring 1,000 inmates of the "Death Camp" near Vaihingen by train to Dachau. These prisoners were moved despite the fact that the incidence of typhus was rising sharply in the camp at the

time of the transfer. In early April the military situation deteriorated rapidly for the Germans, and their attempts to complete the transfer of prisoners were less successful. A train packed with prisoners from Buchenwald took three weeks to reach Dachau, a trip of a few hours' duration in ordinary times. At Flossenbürg the Germans apparently did not have any transport available whatever, and they forced approximately 12,000 of the inmates of that concentration camp to march southward; many fell by the road or were shot if they lagged behind. Discipline finally collapsed when the group was near Cham. The fugitives, many of whom were typhus-infested, scattered into the numerous small towns around Cham.

In the face of the rapid advance of our armies, the Germans then gave up any attempt to move prisoners. After our armored spearheads liberated such places as Dachau and Mauthausen, a short interval elapsed between the removal of the German guards and the arrival of adequate number of our infantry to maintain discipline and control over the camps from the sanitary point of view. In this short interval many louse-infested, typhus-infected inmates "escaped" into the surrounding countryside. I doubt if there ever has been such a widespread scattering of typhus in such a short time as occurred in April and May, 1945, when several of these concentration camps literally exploded into the adjacent areas. In addition to the confusion created by the rapid passage of the war across Germany the situation was further complicated by the floods of persons transplanted by the Germans from the occupied countries into Germany itself for the purpose of working in the German war industries. These people were termed "displaced persons" or "D.P.'s" and their exodus from Germany created an enormous problem, especially from the point of view of typhus control. Typhus had been seeded among some of the groups of D.P.'s prior to the arrival of the Allied armies on the scene. They were further exposed to infection by contact with liberated but undeloused concentration camp inmates who were likewise seeking the quickest way home and mixing with the countless streams of displaced persons in their informal roadside camps.

In the light of this information, one wonders why the figures for the incidence of typhus in 1945 were not very much larger than those reported in Table 1, and why typhus has not been a serious problem again this winter in the same areas, only a few months after the cessation of hostilities. Those who participated in the recent developments in typhus control are convinced that the control program which was worked out by the early part of 1944 was highly effective in suppressing the outbreaks of typhus to which it was applied in Italy,²⁴ Yugoslavia, Germany and Austria in the zones occupied by the Allies. (What has occurred in the Russian areas is not known, since the Russians have not made available the official figures for typhus since 1938.) Before describing the new control methods, I wish to emphasize the fact that

several groups have participated actively in this recent work on typhus: the National Research Council, the medical departments of the Army and Navy, the United States Public Health Service, the United States Department of Agriculture, The Rockefeller Foundation, the United States of America Typhus Commission, the Connaught Laboratory in Canada, the National Institute for Medical Research, members of the Pasteur Institutes in Algeria, Tunisia, Morocco, and Paris, many medical officers in the British and French armies, the officials of the ministries of health in Mexico and Egypt.

DEVELOPMENTS IN METHODS OF LOUSE CONTROL

Early in 1942 two groups in America took up an intensive search for more practical methods of louse control: the entomologists of the Bureau of Entomology and Plant Quarantine of the United States Department of Agriculture, and staff members of the International Health Division of The Rockefeller Foundation. Antilouse powders suitable for application to the clothing were developed and tested in Florida²⁵ and also in New Hampshire.²⁶

In December, 1942, the United States of America Typhus Commission was created by executive order of the President "to formulate and effectuate a program for the study of typhus fever and the control thereof, . . ."²⁷ In 1943 both the Typhus Commission and The Rockefeller Foundation undertook field trials of newly devised antilouse powders in Egypt,^{28,29} Mexico,³⁰ and North Africa.³¹ By the end of 1943 methods for the application of these powders had been worked out^{29,31} whereby large numbers of people could be treated without removing their garments. The powder was shown to be effective when blow into the hair, up the sleeves, down the neck, around the waist into trousers.

The first antilouse powders had pyrethrum as one of the principal ingredients. Such powders had certain disadvantages. The supply of pyrethrum was limited, and the effect of the powder containing it was of relatively short duration. There was, therefore, an urgent need for a synthetic substance, easy to manufacture, safe to use on human skin, and long lasting in its effect as an antilouse powder. The now famous insect killer, DDT, dichloro-diphenyl-trichloroethane,²⁵ proved to be nearly the ideal substance. It had been synthesized by a German student in 1874, but its usefulness was not appreciated until a Swiss firm discovered its insecticidal properties. Wiesmann of the Swiss Agricultural Experiment Station in co-operation with this firm, demonstrated that DDT could be used for the control of certain agricultural pests and houseflies.³² In 1942 the American branch of this company received a sample of DDT as a spray called Gesarol Insecticide. The material was promptly sent to the United States Department of Agriculture, whose entomologists elucidated the remarkable destructive effect of the compound on lice.²⁵ The Food and Drug Admin-

istration of the National Institute of Health carried out toxicological tests and gave the verdict that the material was safe for use as a powder. Although the manufacture of DDT involved some critical materials and equipment, shortly several plants were producing large amounts for the use of the armed forces. The most satisfactory property of DDT is the persistence of its lethal effect on lice for more than two weeks when dusted into the garments, or for several weeks when impregnated from an emulsion. Reinfestation of dusted persons exposed to louse-infested persons was reduced to a negligible degree by this persisting effect of DDT.

The final improvement in delousing technique was the development by the Army of an air compressor which operates ten dust guns simultaneously. These devices are called power dusters. They use gasoline for fuel and are very simple to operate. By employing power dusters it was possible to delouse more effectively the streams and floods of displaced persons who were pouring out of typhus-infested areas in Germany and Austria as our armies liberated them. The power dusters were placed on the east bank of the Rhine River at the pontoon bridges where the displaced persons were crossing; they were taken by truck to the concentration camps, to the displaced persons centers, to the prisoner of war camps, and to the villages in southern Germany where secondary cases of typhus were found.

The results of this vigorous delousing campaign were highly gratifying to those responsible for typhus control in the European theater. Relatively few persons crossed the Rhine barrier into Western Europe without being deloused with DDT, despite the suddenness with which many millions of persons had to be processed. The many typhus outbreaks all over Germany were promptly handled, and secondary cases in these foci were remarkably few. I believe that this reflects great credit on those who were responsible for the excellent way in which the typhus control program was organized. That the necessary supplies were present on the scene in adequate amounts is likewise a tribute to their foresight and persistence. They made possible this demonstration that typhus can be controlled quickly under very adverse circumstances by skillful organization in the application of the new methods of delousing. However, there may yet be severe outbreaks of typhus before the war-torn areas have returned to a more normal state of affairs if the authorities who are responsible for public health in occupied areas do not remain fully alert to the danger of typhus and do not provide adequate amounts of typhus control supplies wherever the need for them may arise.

The yolk sac typhus vaccine devised by Cox was taken to Bolivia and to Spain in 1941 in attempts to evaluate it under epidemic conditions,^{33,34} but these trials were without conclusive results. Several cases of typhus had occurred among physicians who had been vaccinated and exposed to the disease

in the laboratory. It seemed probable that their illnesses had been made less severe by the vaccine, but further improvements were sought. To this end it was decided to increase the rickettsial content of the vaccine and to introduce certain changes in the methods of preparation intended to improve the potency and facilitate large scale production.^{35,36} In addition to these changes a much more satisfactory method for potency testing of typhus vaccines was introduced in 1942.³⁶ The very difficult feat of producing millions of doses of Cox type vaccine was accomplished in a relatively short time by several of the commercial firms under contract with the government.*

Thus a prodigious amount of typhus vaccine was made available for the first time. There was enough to immunize all of our troops who were sent to areas where they might be exposed to epidemic typhus, and to administer booster doses at proper intervals while the danger of exposure existed. There was enough to permit distribution for use in the armed forces of our Allies and for use in civilian populations in certain of the danger zones.

The value of Cox type vaccine was demonstrated in the study undertaken by the United States Typhus Commission in cooperation with the Egyptian Ministry of Health in Cairo in 1943. There were 40,000 cases of epidemic typhus in Egypt in 1943, and several thousand patients were admitted to the Cairo Fever Hospital. Many new employees were added to the staff to handle this large increase in patient population. Typhus in previous years had been characteristically severe among the Fever Hospital employees, and those who contracted the disease in 1943 and 1944 without having been vaccinated were likewise severely stricken. Most of the employees, however, were vaccinated by the Typhus Commission in that period. It should be stressed that these employees were exposed to typhus not only in their hospital duties but also as residents in the areas of Cairo where the typhus attack rate was high. There were 61 cases of typhus among the vaccinated employees in the two seasons, and of this group only one patient died, a man whose first dose of vaccine was given just three days before the onset of illness. Those who had had their vaccine more than 21 days before the onset of illness had mild, uncomplicated typhus of short duration.³⁷ From these observations made under actual epidemic conditions, it thus appeared that Cox type vaccine of acceptable potency practically eliminated the mortality from typhus fever and rendered the illness mild and of short duration.

There is another important aspect of typhus vaccine from the point of view of the possibility of spread of the disease in a louse-infested community. The lice which feed on patients who contract typhus after a course of typhus vaccine develop very few rickettsiae in comparison with lice from unvaccinated patients. Persons who have had

booster doses infect their lice only rarely or not at all.^{38,39,40} Thus vaccination of a community undoubtedly will reduce the potentiality for spread of the disease by lice.

In addition to the studies in the Cairo Fever Hospital the experience of our armed forces contributes some evidence for the effectiveness of Cox vaccine. I have already called attention to the high incidence of typhus in the regions into which our armies were sent between 1942 and 1945. Official figures have not been released by the War Department, but I am permitted to say that there have been fewer than 100 proven cases of classical epidemic typhus fever in our armed forces during the second World War. There have been no deaths from typhus among our forces, and indeed no authentic record has come to our attention of a death from typhus after Cox vaccine, administered more than 21 days before the onset of illness. In contrast, we may point out that 200 cases of proven typhus in the British forces were mentioned by van Rooyen,⁴¹ and 21 cases with seven deaths were described by Stevens.^{42**} These reports refer to the period before general antityphus vaccination was adopted by the British forces.

It seems safe to assert on the basis of the information now available that Cox type vaccine when properly prepared and administered will reduce the mortality from typhus to a negligible point, will lessen the severity of the illness greatly, and should decrease enormously the possibility of typhus attaining epidemic proportions in a thoroughly vaccinated community.

DEVELOPMENTS IN THE THERAPY OF TYPHUS FEVER

Developments in the therapy of typhus have been made in two directions: first, as regards a better understanding of the pathologic physiology of the disease, and second as regards specific sero- or chemotherapeutic agents. In the first category belong the observations on the presence and importance of azotemia in typhus fever.^{43,44} It was noted as long ago as 1862 that the blood urea nitrogen was increased in typhus fever, and several reports are in the literature confirming this finding. By careful observation of the patients on the Typhus Commission ward in the Cairo Fever Hospital during three seasons it has been possible to advance our understanding of this phenomenon.^{43,45} It was apparent that the development of renal insufficiency was one of the earliest indications that the course of the illness would be very severe or even fatal.

** When this article was in preparation, the following statement appeared: "In the winter and spring of 1942-43 typhus was epidemic in North Africa and there were hundreds of thousands of instances of the disease in the civilian population. Among American Army personnel who had been immunized and reimmunized with the Cox type of typhus vaccine only two mild cases of the disease were recorded in the first four months of 1943, while during the same period in a comparable group of Allied troops among whom vaccination was not initiated until the end of February or the first of March, 1943, a total of 43 cases were recorded, with a case fatality rate of roughly 30 per cent." Long, P. H., J.A.M.A., 130:985, 1946.

* Cox himself played an important rôle in this respect.

Several factors may participate in the development of renal insufficiency in typhus. There may be damage to the kidneys produced by growth of rickettsiae in those sites. A rapid drop in systolic blood pressure of a few hours' duration or longer may initiate serious changes in the kidney as a consequence of reduced renal blood flow in the period of hypotension. Severe dehydration may exaggerate the situation. It is difficult to evaluate these factors individually. They are not all uniformly present in the patients who develop renal insufficiency, but by directing supportive measures to reduce their influence as much as possible, the patients may be appreciably benefited. For example, careful attention to the fluid intake and output makes it possible to reduce the extent of dehydration and to assure an adequate urine volume. The drop in systolic blood pressure which is of such serious prognostic import may be attacked by prompt administration of plasma intravenously.

In the other category, that of specific therapeutic agents, a considerable list of substances received attention in the war years. I shall mention just a few of these, and then discuss in some detail the one which seems to me to offer the most promise at present in the treatment of typhus—the chemical, para-aminobenzoic acid.

Hyperimmune refined and concentrated anti-typhus rabbit serum, prepared in the same way that the antipneumococcus rabbit serum was produced,⁴⁶ was administered to typhus patients in Egypt^{42,47} and in Germany.⁴⁸ In the first few days of illness large amounts of serum seemed to modify the course of the infection, but the effect was less striking in patients who had been sick nearly a week.

An antimalarial drug called sontoquine was used in typhus by French physicians who felt that it exercised a beneficial influence on the clinical picture.⁴⁹ The Germans were impressed by the drug called rutenol, which is a combination of a nitro-acridin derivative and arsenic acid.⁵⁰ The English workers found a drug, para-sulphonamidobenzamide, which had strongly antirickettsial effects in experimental typhus, but the clinical trial was disappointing.^{51,52} Penicillin was found to have some antirickettsial activity in experiments with eggs and mice,⁵³ but a thorough clinical trial was not carried out on typhus patients. Toluidine blue and a drug called forbisen were shown to be of some value against experimental typhus,⁵⁴ but these substances were not given clinical trial. The common dye methylene blue was found by three groups of workers to possess activity against rickettsiae of tsutsugamushi disease,^{55,56,57} and when given in large amounts, against typhus also.⁵⁵ Clinical trial in Burma by a United States Navy group indicated that methylene blue was difficult to give in adequate amounts by the oral route. Despite its toxicity it seemed to be of benefit by the intravenous route.⁵⁸

The substance which seems to offer promise in the treatment not only of typhus but also of tsutsugamushi disease and perhaps Rocky Mountain

spotted fever as well, is para-aminobenzoic acid, which is referred to as PABA. The effect of this substance in experimental murine typhus was first noted in 1942 in The Rockefeller Foundation laboratory in New York City.⁵⁹ Its activity was independently discovered in 1944 by Greiff, Pinkerton, and Moragues.⁶⁰ PABA was given to patients in Egypt⁶¹ in 1943, 1944, and 1945. In Germany it was used in an attempt to alleviate the severity of the typhus outbreak at the concentration camp at Dachau in 1945.⁴⁸ PABA was shown to be effective against experimental tsutsugamushi disease^{62,63} and in a clinical study in Burma.⁶⁴ In 1945 workers in Texas⁶⁵ and in the Army Medical School⁶⁶ found that PABA has activity against spotted fever. One human case of proven Rocky Mountain spotted fever has been treated with therapeutic amounts of PABA with apparent benefit.⁶⁷ Thus this agent seems to have possibilities for the treatment of at least four different rickettsial infections of man. It now has been given in large amounts to more than 100 patients and appears to be entirely safe for human use.⁶⁸ Precautions are taken to follow the white blood cell count, which tends to be depressed by the drug, and to measure the pH of the urine at frequent intervals. It is important to adjust the intake of bicarbonate to keep the urine neutral or alkaline in reaction to prevent formation of crystals of PABA in the kidneys. Experimental evidence suggests that larger concentrations of PABA are required for an effect against tsutsugamushi disease than for typhus.⁶⁹ Rocky Mountain spotted fever may be found to respond to smaller concentrations than typhus,⁶⁶ although that should be labeled as speculation at this time.

PABA seems to arrest the progress of typhus and to permit the immunity mechanisms of the host to deal with the rickettsiae. Direct contact of the organisms with the same concentrations of PABA which are attained in the blood of patients has no apparent effect on either the viability of the rickettsiae or on their toxic properties.⁶⁹ It seems probable that PABA acts by inhibiting the multiplication of rickettsiae inside the cells. Whether it affects primarily the chemical processes in the cytoplasm of the host cells or whether it interferes with the processes which take place inside the rickettsiae themselves is not known.

There is no evidence that PABA will benefit patients who have been ill longer than seven days at the time treatment is first started. When treatment is started before the end of the first week of illness there seems to be a significant correlation between the duration of fever and the incidence of complications on the one hand, and the length of time between onset of illness and beginning of treatment. It is very difficult to make a diagnosis of typhus definitely before the appearance of the characteristic rash on the fourth or fifth day. In using PABA the effort must be made to start administration of the drug as soon as the diagnosis of typhus is suspected or established. A more thorough appreciation of the value and limitations of

PABA as a therapeutic agent must be derived from more extensive clinical experience.

SUMMARY

In the past typhus fever has been one of the most feared of the epidemic diseases associated with wars and human misfortunes. In the second World War several new methods of controlling the disease were applied successfully to the outbreaks in Italy, Yugoslavia, Germany, and Austria. In the technique of delousing, a method has been developed for application of antilouse powder directly to the clothes of louse-infested persons, without requiring them to remove their garments. The chemical DDT has been applied on a large scale and has been found to be safe and effective as a delousing agent. Power dusters using DDT powder have greatly increased the efficiency and the scope of the delousing process. Vaccine of the Cox type has been produced in huge quantities and has been used successfully by our armed forces. Our information bearing on clinical aspects of the disease has been advanced, and a new drug, para-aminobenzoic acid, has been found to offer promise in the treatment not only of typhus fever but of other rickettsial infections as well.

The conclusion may be drawn that our knowledge of typhus has been extended in several fields and that, if our information is properly applied in the future, classical epidemic typhus fever will not cause the suffering and loss of life which it did in the past.

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